

CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

#351
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TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

Date: April 20, 1962

1. Name of Investigator: SIMON H. WENDER, Ph.D.
2. Title: Studies on Polyphenols of Cigarette Smoke
3. Institution & Address: University of Oklahoma Research Institute
Office of Executive Director
Norman, Oklahoma
4. Project or Subject: On this project, we shall undertake the identification of individual polyphenolic compounds present in the smoke from cigarettes and the preparation, where feasible, of these compounds for studies on their metabolism and possible effect on human health.

5. Detailed Plan of Procedure:

Our present studies on cigarette smoke will be expanded in an effort to isolate and identify the many individual polyphenols present. These include the large group of phenolic acids that our laboratory was the first to discover as being present in cigarette smoke and also still another group of compounds recently discovered in cigarette smoke in our laboratory, and as yet not reported. The latter apparently contains aromatic aldehydes. No previous report on either group has appeared in the literature.

Extensive paper and column chromatography, infrared and ultraviolet spectrophotometry, and spectrophotofluorimetry will be utilized.

Certain polyphenols, such as rutin and chlorogenic acid, are known to be present in relatively larger amounts in cigarette tobacco. In such cases, dry samples of each will be heated strongly, and the resulting substances will be analyzed for possible clues as to what their breakdown products might be in cigarette smoke. We have initiated such studies in our laboratory with very promising preliminary results.

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Procedures for synthesizing sufficiently large amounts of a polyphenol for biological studies will be developed, where literature reports have indicated possible effects of such a compound on animal health. In some cases, it is anticipated that such polyphenolic compounds may be synthesized to contain a specifically labeled atom such as carbon 14, in order to investigate more effectively the fate of these compounds in the smoke from cigarettes, and also their biological pathway. And if T.I.R.C. so suggested, such compounds could be studied biologically in cooperation with workers at the University of Oklahoma School of Medicine. Research on the synthesis of radioactive scopoletin is definitely to be done.

PREVIOUS WORK

Wender and co-workers have purified and identified quinide (gamma lactone of quinic acid) and also quinic acid on paper chromatograms of extracts of mainstream cigarette smoke (Journal of Organic Chemistry, 26, 3017 (1961). Also, Wender's group has identified esculetin (6,7-dihydroxycoumarin) (J. Org. Chem. 24, 1134 (1959), scopoletin (6-methoxy-7-hydroxycoumarin) (J. Org. Chem. 23, 204 (1958), and cis - and trans - caffeic acids (J. Org. Chem. 25, 658 (1960) in the mainstream smoke from cigarettes. Quantitative methods for the determination of scopoletin in tobacco smoke and in tobacco products have been developed by these University of Oklahoma scientists (Anal. Chem. 30, 2041 (1958)).

In cooperation with Mr. Marvin Shetlar of the University of Oklahoma School of Medicine and students, studies have been undertaken on the fate of esculetin, scopoletin, and quercetin (3,3', 4',5,7-pentahydroxyflavone) in the laboratory rat (Arch. Biochem. and Biophys. 75, 538 (1958); 81, 430 (1959); 85, 264 (1959); and Biochim. et Biophys. Acta. 44, 606 (1960)).

An improved synthesis of scopoletin has been devised (Biochim. et Biophys. Acta. 44, 163 (1960)).

Although no other laboratory has reported the identification of any polyphenolic acids in cigarette smoke, Yang and Wender have recently identified twelve phenolic acids in cigarette smoke (Journal of Chromatography, in press). They are m-hydroxybenzoic, p-hydroxybenzoic, protocatechuate, vanillic, syringic, o-hydroxyphenylacetic, p-hydroxyphenylacetic, m-hydroxyphenylacetic, cis- and trans-p-coumaric, cis- and trans-ferulic, m-hydroxyphenylpropionic, and p-hydroxyphenylpropionic acids.

6. Budget Plan:

(One Ph.D. full-time plus one M.S. or Ph.D. part-time)	a. Salaries	\$11,800.00
	b. Expendable Supplies	1,100.00
	c. Permanent Equipment	None
	d. Overhead (15% of a,b,e)	2,060.00
	e. Other*	850.00
TOTAL		15,810.00

*O.A.S.I., reprints, travel, fringe benefits when applicable.

7. Anticipated Duration of Work: THREE (3) Years
8. Facilities and Staff Available: Adequate research facilities for the proper prosecution of the investigation are available.

Dr. Chao-Hwa Yang, who isolated and identified the phenolic acids, scopoletin, etc. in cigarette smoke, is available for the full-time Ph.D. position. Mr. Alex Zane, M. S. in Chemistry, is now working part-time on the pyrolysis products of rutin, and should be available for the other position.

9. Additional Requirements: NONE

10. Additional Information (Including relation of work to other projects and other sources of supply):

Similar research on the polyphenols in cigarette smoke has been supported by the National Institutes of Health for the past three years (\$55,168). The N. I. H. project expires August 31, 1962. Prior to that, support was kindly furnished by the Tobacco Industry Research Committee.

Signature SIMON H. WENDER
Director of Project

CHARLES S. STANDLEY
Business Officer of Institution

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